REMARKS

This case contains claims 1-3 with the entry of this Amendment. New claim 2 is supported by the Specification, at page 4, lines 1-30. New claim 3 is supported by the Specification, at page 5, lines 1-4. The amendments made in the Specification represent the deletions of the reference numbers. Therefore, none of the amendments made herein constitutes the addition of new matter.

The Rejection under 35 U.S.C. 103:

Claim 1 is rejected under 35 U.S.C. 103(a) as unpatentable over Gething et al. (U.S. Patent No. 5,041,376) in view of Lollar (U.S. Patent No. 5,859,204). Applicant respectfully traverses this rejection.

The Patent Office alleges:

> Gething et al. teach a method of preparing proteins having modified glycosylation by mutating the protein to encode an N-linked glycosylation site (N-X-S/T) and expressing the mutant protein in a host cell capable of post-translational glycosylation whereby the protein with the modified glycosylation is prepared. Gething et al. suggest that almost any protein could be used in the disclosed method. Gething et al. states ....that mutant proteins produced in the disclosed method are less likely to induce an immune response than other proteins that have been altered by genetic engineering.....
>
> Gething et al. do not disclose that factor VIII specifically could be used in the method.
>
> Lollar teaches site-directed replacement of specifically defined amino acids in human factor VIII can result in reduction of reactivity to an inhibitory antibody. Lollar states that at the time of the present invention, it was commonly known that there is a significant interest in the development of a factor VIII that is less apt to cause production of inhibitory antibodies and a factor VIII molecule that evades immune detection in patients who have already acquired antibodies to human factor VIII.
>
> Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to add N-linked glycosylation sites by site directed mutagenesis as taught in Gething et al. to the factor VIII molecule.

Applicant points out that the claimed invention was made possible due to the inventor's unique insight in recognizing the problem of the development of inhibitory antibodies to factor VIII in patients with hemophilia, and applying the scientific knowledge that the immunogenicity can be reduced by altering the epitope by glycosylation to solve that problem. Without the combination of these two factors, the claimed invention could not have been made. This is particularly true in the present case because the Gething et al. reference does not teach or suggest the necessity of altering factor VIII for reduced immunogenicity. Gething et al. is a general reference simply makes a statement that almost any protein could be used in the disclosed method. However, unless one had a compelling reason to use the method in Gething et al. to modify factor VIII as the present inventor did, one of ordinary skill in the art would not have been motivated to modify factor VIII as claimed in the present invention.

Contrary to the Examiner's allegation, Lollar does not suggest or motivate one of ordinary skill in the art to make the claimed invention. Lollar teaches site-directed replacement of specifically defined amino acids, residues 484-509, in human factor VIII to reduce reactivity to an inhibitory antibody. Any residues between 484-509 can be replaced randomly by site-directed mutagenesis with non-antigenic amino acid sequence, e.g., alanine or replacement of specific amino acid residues of the factor VIII of one species with the corresponding unique amino acid residues of the factor VIII of the other species. This domain was chosen based on the observation that the pig factor VIII is less immunogenic in human patients and on domain and sub-domain substitutions of porcine factor VIII segments for human factor VIII which led to identification of binding site for certain inhibitory antibodies (see Table 1). Lollar does not teach or suggest that any specific domains or residues in human factor VIII can be modified to reduce reactivity to an inhibitory antibody. There is no teaching or suggestion in the Lollar reference that a method other than a random replacement of an amino acid residue by site-directed mutagenesis would be useful for human factor VIII to reduce immunogenicity. Nothing in Lollar suggests that the immunogenicity can be reduced by altering the epitope by glycosylation of the factor VIII.

Applicant submits that the allegation by the Examiner that it would have been obvious to one of ordinary skill in the art at the time of the invention to add N-linked glycosylation sites by site directed

mutagenesis as taught in Gething et al. to the factor VIII molecule, is based on hindsight. The courts have given repeated reminders as to the impermissible use of hindsight in constructing a rejection for obviousness and the necessity that the cited references themselves provide the motivation for their combination. See, for example ACS Hospital Systems, Inc. v. Montfiore Hospital, Inc., 221 U.S.P.Q. 929, C.A.F.C., 1984; *In re Jones*, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) ("Before the PTO may combine the disclosures of two or more prior art references in order to establish prima facie obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art."); Northen Telecom, Inc. v. Datapoint Corp., 15 U.S.P.Q. 2d 1321, 1323 (Fed. Cir. 1990) ("It is insufficient that the prior art disclosed the components of the patented [invention], either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor."); *In re Oetiker*, 24 U.S.P.Q. 2d 1443 (Fed. Cir. 1992) ("[t]here must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination" and "[t]hat knowledge can not come from the applicant's invention itself."); and In re Dow Chemical Co., 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.... Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.") The Patent Office "cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention." Smithkline Diagnostics, Inc. v. Helena Laboratories Corp., 8 U.S.P.Q. 2d 1468, 1475 (Fed. Cir) 1988).

In particular, it is unclear how one skilled in the art could make the leap from altering glycosylation of a virus coat (Gething et al.) to modify glycosylation of a physiological human protein except by hindsight. Furthermore, the long gap from Gething's publication (Gallagher et al. (1988 Dec) "Addition of carbohydrate side chains at novel sites on influenza virus hemagglutinin can modulate the folding, transport, and activity of the molecule" *J Cell Biol.* **107**:2059-73, attached hereto as Exhibit A) to the present invention indicates that those skilled in the art did not, in fact, make the connection, despite the long-felt need for a factor VIII with reduced antigenicity (Lollar and Runge, U.S. Serial No. 07/864,0 04 filed in April 7, 1992). Therefore, objective criteria of unobviousness

combined with the scientific criteria point in the same direction -- that the invention is not obvious in view of the cited art.

In summary, based on the foregoing discussions, applicant submits that the claimed invention is a result of inventor's own unique insight in combining the necessity of a less immunogenic factor VIII and the scientific knowledge that the immunogenicity can be reduced by modifying the epitope by glycosylation of the factor VIII. Therefore, claim 1 is not *prima facie* obvious over the prior art and withdrawal of the rejection under 35 U.S.C. 103 is respectfully requested.

In conclusion

Based on the foregoing amendments and arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This amendment is accompanied by a Petition for Extension of Time (three months) and a check in the amount of $890.00 as required under 37 C.F.R. 1.17(a)(3) for a large entity. If the amount submitted is incorrect, however, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,

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The following is the second paragraph starting line 1, page 1.

Hemophilia A is defined as hereditary deficiency of blood coagulation fVIII. fVIII is synthesized as a ≈300 kDa single chain protein with internal sequence homology that defines the "domain" sequence NH_2-A1-A2-B-A3-C1-C2-COOH (Fig. 1) [<{{33}}>]. Domains are commonly delineated as A1 (Ala1-Arg372), A2 (Ser373-Arg740), B (Ser741-Arg1648), and A3-C1-C2 (Ser1690-Tyr2332) [<{{398}}>]. Despite its large size, the B domain of fVIII has no known function and can be deleted [<{{11}}>]. fVIII is measured by its ability to correct the prolonged clotting time of plasma prepared from patients with hemophilia A.

The following is the fourth paragraph starting at line 15, page 1.

The development of inhibitory antibodies (inhibitors) to fVIII is a serious complication in the management of patients with hemophilia A. Alloantibodies develop in approximately 25% of patients with hemophilia A in response to therapeutic infusions of fVIII [<{{2193}}>]. In previously untreated patients with hemophilia A who develop inhibitors, the inhibitor usually develops within one year of treatment [<{{2105}}>], although it can occur at any time [<{{2137}}>]. Additionally, autoantibodies that inactivate fVIII can occur in non-hemophiliacs in a variety of clinical settings including the postpartum period, in systemic lupus erythematosus, in chronic lymphocytic leukemia, and in elderly females. This condition is called acquired hemophilia.

The following is the second paragraph starting at line 7, page 2.

fVIII inhibitors are measured clinically by the ability of the patient's plasma to inhibit fVIII in normal plasma. The standard test is the Bethesda assay [<{{1806}}>]. One Bethesda unit is defined as the dilution of patient plasma required to reduce the fVIII level by 50%.

The following is the third paragraph starting at line 11, page 2.

A molecule is said to be *antigenic* when it binds to antibodies and *immunogenic* when it can induce an immune response [<{{1895}}>]. The immunogenicity of a molecule depends on the B cell repertoire, T cell help and suppression, and the major histocompatibility complex, which together determine the concentration and binding affinity of antibodies for an antigenic site. If a fVIII molecule could be constructed that did not bind to the inhibitory antibodies in a patient's plasma, it would useful therapeutically. Additionally, if a fVIII molecule could be constructed that is less immunogenic than wild-type human fVIII, i.e., could significantly lower the 25% incidence of inhibitor development, it would be safer than wild-type human fVIII. This molecule would have general applicability in the hemophilia A population.

The following is the fourth paragraph starting at line 21, page 2.

Inhibitory antibodies to fVIII bind to either the A2, A3, or C2 domains of fVIII and disrupt specific functions associated with these domains [<{{57,595,1803}}>]. The A2 epitope is located within a linear sequence bounded by residues Arg484-Ile508 [<{{2054}}>]. The C2 epitope has been localized to a sequence bounded by residues Glu2181-Val2243 [<{{2574}}>]. The A3 epitope has not yet been mapped. The fact that fVIII epitopes are limited in number and can be mapped to the amino acid sequence level makes it possible to design strategies to produce low antigenicity and low immunogenicity fVIII molecules. We have already reduced the antigenicity of fVIII by replacing epitopes with non-human fVIII sequences [<{{1824,2054,2574}}>] and by site-directed mutagenesis of amino acids within fVIII epitopes [<{{2343}}>].

The following is the first paragraph starting at line 1, page 3.

Viruses, such as the human immunodeficiency virus (HIV), elude the immune system by varying epitopes that are recognized by antibodies [<{{2573}}>]. HIV contains an exterior envelope glycoprotein, gp120, which is targeted by the immune system in its attempts to rid the body of virus. HIV reduces the immunogenicity of gp120 using a post-translational process in which a polysaccharide is linked to asparagine residues. This process is called N-linked glycosylation because N is the single letter code for the amino acid asparagine. When the immune system makes antibodies to the existing glycosylated epitope, HIV responds by mutation vary its N-linked glycosylation sites. This reduces the immunogenicity of the virus. Similarly, the immunogenicity of fVIII could be reduced by altering the epitope by glycosylation. Additionally, the structure recognized by existing antibodies would be altered, reducing the antigenicity of the molecule.